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Original Article

Evaluation of left ventricular mechanical dyssynchrony with phase analysis in end-stage renal disease patients with normal gated SPECT-MPI

ABSTRACT

Phase analysis using gated single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) is a relatively new tool for the assessment of ventricular synchrony. Hypertension, diabetes, renal diseases, and dyslipidemia may affect the phase parameters though their impact is not well understood. The present study aimed to evaluate the incidence of the left ventricular mechanical dyssynchrony (LVMD) in end-stage renal disease (ESRD) patients with normal gated SPECT-MPI and QRS duration (<120 ms) on electrocardiogram. Data of 129 patients (86 males) referred for gated SPECT-MPI for their pretransplant evaluation with normal gated stress SPECT-MPI (SSS <3 and ejection fraction 50%) were included in the study analysis. Documented clinical history along with confounding factors such as hypertension, dyslipidemia, smoking, and alcoholism were evaluated. Left ventricle functional (end-diastolic, end-systolic, and LV myocardial volume) and phase parameters (phase standard deviation [PSD], phase bandwidth [PBW] and entropy) were calculated using the QPS-QGS program. LVMD was noted in 36 (28%) of ESRD patients with normal QRS duration and gated SPECT-MPI. The mean attenuated corrected LV myocardial volume, ejection fraction, mean PSD, and PBW values were 84.3 ± 38.1 ml, 65.3 ± 13.5%, 9.8 ± 3.9 , and 61.4 ± 24.7 , respectively. The LV myocardial volume shows statistically significant correlation with the phase parameters (r = 0.31–0.47; P < 0.001). LVMD is present in a significant number of ESRD patients, and its extent is more with increase in LV myocardial volume. It may have an additional role in risk-stratification for cardiovascular disease in ESRD patients.

Keywords: End-stage renal disease, gated single-photon emission computed tomography myocardial perfusion imaging, left ventricular dyssynchrony, phase histogram bandwidth, phase standard deviation

INTRODUCTION

The end-stage renal disease (ESRD) patients with cardiovascular disease have a poor prognosis and is one of the leading causes (contributing around 45%) of premature deaths. Some authors consider ESRD patients as coronary artery disease (CAD) risk equivalents.[1,2] In a meta-analysis of nine studies, the commonly employed stress myocardial perfusion imaging in chronic kidney disease patients (potential kidney transplant recipients) had shown a wide range with pooled sensitivity and specificity of only 74% and 70% respectively for detecting the significant CAD that would even be lower in ESRD patients.[3] There is a need for additional markers in ESRD cohort to improve the accuracy of single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI). Cardiac dyssynchrony might be a potential marker contributing to the high incidence of sudden cardiac deaths in ESRD patients.[4,5] Cardiac dyssynchrony is the uncoordinated, asynchronous contraction of myocardial muscles which may occur either

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due to electrical dyssynchrony (QRS >120 ms) or contractile disparities also known as mechanical dyssynchrony.[6] Patients with left ventricular mechanical dyssynchrony (LVMD) have independently increased mortality risk compared to the general population.[7] LVMD reduces cardiac systolic function with increased oxygen consumption and later on may lead to arrhythmia as a complication. LVMD has been shown to strongly correlate with cardiac hemodynamic parameters and adverse cardiac events.[8,9] The gated SPECT-MPI is one of the noninvasive imaging methods which offers a fully automated and reproducible way to perform the phase analysis for assessment of LVMD from the generally available SPECT-MPI data in addition to simultaneous assessment of LV myocardial ischemia/scar and functional parameters.[10-13] LVMD may serve as a predictive factor of both the cardiac outcome and all-cause mortality in ESRD patients.[14] The aim of the present study was to evaluate the prevalence of LVMD in ESRD patients with normal gated SPECT-MPI and QRS duration on the surface electrocardiogram.

METHODS

The study population consisted of patients with ESRD who underwent stress SPECT-MPI as a part of their prerenal transplant evaluation. The patients with normal gated myocardial perfusion imaging findings (SSS <3 and LV ejection fraction ≥50%) and narrow QRS duration (<120 ms) were included in this study. Patients with diabetes mellitus, known cardiac disease, perfusion defect(s), arrhythmia on gating, and wall motion abnormality in gated stress SPECT-MPI were excluded from the study. This retrospective, observational, and nonexperimental study was carried out in the nuclear medicine department of tertiary care institute. The study was duly approved by the Institute Ethics Committee vide letter No. INT/IEC/2018/000335.

Gated myocardial perfusion single-photon emission computed tomography acquisition

All patients underwent ^{99m}Tc-sestamibi 1-day stress-first or stress only gated SPECT-MPI protocol according to the American Society of Nuclear Cardiology guidelines routinely followed in our department.[15] Stress was induced with intravenous adenosine infusion at rate of 140 μg/kg/min for 6 min duration and radiopharmaceutical (6.3 MBq/kg body weight) injected at 3rd min in all patients. Gated SPECT-MPI poststress acquisition after a period of 30–45 min was performed on a dual-head camera SPECT/CT system (Philips Bright view XCT, Philips Medical Systems, Milpitas, CA, USA) in the supine position with a low-dose CT scan acquisition for attenuation correction. The rest studies were not performed in this cohort to avoid radiation exposure as poststress studies were normal.

Stress gated images were acquired using a 15% window centered over the 140 KeV photopeak of ^{99m}Tc with parallel hole, low-energy, and high-resolution collimators. The matrix size used was 64 × 64 with maximum zoom of 1.46. Thirty-two projections of 20 s each were taken per head, for a total of 64 images in step and shoot method for 180° orbit starting from 45° right anterior to 135° left posterior. In addition, contour orbit was made in a counterclockwise direction to verify the free execution of the rotation, without touching the patient or the couch.

Phase analysis

The PHASE tool of the QPS-QGS program (version 7.2; Cedars-Sinai Medical Center, Los Angeles, USA) was used for analysis of phase parameters on poststress acquired data. The myocardial surfaces were presented using two dimensional ellipsoidal coordinate systems with 36 longitudes and 28 latitudes leading to 1008 surface sampling points. Myocardial contraction onset time was detected with changes observed in myocardial pulse quantity. The phase standard deviation (PSD), phase bandwidth (PBW), and LV entropy obtained from the phase analysis were evaluated, as they have been shown to identify the LVMD best. PSD represents the heterogeneity of LV myocardial contraction onset times and PBW stands for the distribution of time during which 95% of the LV myocardium starts contraction while LV entropy represents parameter of mechanical synchrony provided by QPS-QGS program, which is normalized to its maximum value and reported as a percentage ranging from 0% to 100% from complete order to disorder.

Statistical analysis

A descriptive analysis was performed using frequencies in the case of qualitative variables. On the other hand, quantitative variables with or without normal distribution (after applying the Kolmogorov–Smirnov normality test), were expressed by means and standard deviation. Correlations between continuous variables (LV volume with PSD, PBW, and entropy) were assessed by the Spearman's Rank correlation test and Pearson coefficient. Statistical analyses were performed using SPSS software (SPSS Version 22.0; IBM Corp, Armonk, NY, USA). The value $P < 0.05$ was taken as the limit to establish statistical significance.

RESULTS

Study population

SPECT-MPI data from 392 patients with ESRD were analyzed retrospectively, and 129 patients (43 female) fulfilled the inclusion criteria for normal gated SPECT-MPI and LV ejection fraction >55%. The studied cohort had a mean age of 43.6 ± 11.7 years with male (67%) predominance. Twenty-three (18%) patients had a

history of alcohol intake while 84 (65%) patients were hypertensive (blood pressure >140/90 mm Hg or on anti-hypertensive drugs) at the time of presentation. Clinical characteristics of the study population are presented in Table 1. For LV functions, the mean ejection fraction was 65.3 ± 13.5%, end-diastolic and end-systolic volumes were 99.9 ± 44.8 and 44.4 ± 28.1 ml, respectively. The mean attenuated corrected LV myocardial volume observed was 84.3 ± 38.1 ml [Table 2].

Phase analysis

The mean values of PSD, PBW, and Entropy observed were 9.80°, 61.36°, and 51.88% respectively which were significantly higher ($P < 0.01$); [Table 3] compared to the control population (nondiabetic and nonchronic kidney disease patients with normal gated SPECT-MPI, the said data had been published previously).[16]

Based on the cutoff value (greater than mean + 2SD) derived from control population in QPS-QGS program (11.7° and 45.6° for PSD and PBW, respectively), LVMD was observed in a significant number (36; 28%) of patients with ESRD. Figure 1 shows the dataset of ESRD patient with normal gated SPECT-MPI and significant LV dyssynchrony. The PSD showed a significant negative correlation with the LV ejection fraction ($r = -0.63$; $P < 0.001$) while statistically significant positive correlation was observed with the end-systolic volume ($r = 0.56$; $P < 0.001$) and end-diastolic volume ($r = 0.42$; $P < 0.001$) [Figure 2]. These LV functional parameters show similar correlation with other phase parameters (i.e., PBW and entropy) also. Furthermore, scatter plots were drawn to find the correlation between attenuated corrected LV myocardial volume and phase parameters. The attenuated-corrected LV myocardial volume shows a statistically significant correlation with all the phase parameters (PSD, PBW, and entropy) with *r* value ranging from 0.31 to 0.47 [Figure 3].

Table 1: Baseline characteristics of the study population

Clinical characteristics	Value (%)
Age (years)	43.6±11.7
BMI (kg/m²)	21.9±5.3
Male	86 (67)
Obese	11 (08)
Hypertension	84 (65)
Alcoholism	23 (18)
Smoker	20 (15)
Dyslipidemia	15 (12)

Except for age and BMI, the rest of the variables are expressed as the number of patients with percentage in parenthesis. Age and BMI are expressed as mean±SD. BMI: Body mass index; SD: Standard deviation

Table 2: Left ventricle quantitative parameters of the end-stage renal disease patients

LV parameters	Mean±SD	Range
Ejection fraction (%)	65.31±13.5	50-99
EDV (ml)	99.93±44.8	24-223
ESV (ml)	44.45±28.1	1-131
Myocardial volume (ml)	84.3±38.1	23-199

LV: Left ventricular; EDV: End-diastolic volume; ESV: End-systolic volume; SD: Standard deviation

Table 3: Phase analysis data in the end-stage renal disease patients and its correlation with control population

Phase parameters	ESRD patients (*n*=129)	Controls (*n*=132)*	*P*
PSD°	9.80±3.9	6.64±2.5	<0.01
PBW°	61.36±24.7	26.20±9.7	
Entropy (%)	51.88±8.5	45.08±6.3	

*Data had been published (16). ESRD: End-stage renal disease; PSD: Phase standard deviation; PBW: Phase bandwidth

DISCUSSION

Numbers of ancillary markers along with SPECT-MPI have been used for better prognostication and risk stratification in patients with suspected or diagnosed CAD; however, only few of them had been tested in the ESRD cohort. The additional markers may be useful in these high-risk patients given the low sensitivity and specificity of SPECT-MPI. The present study examined the prevalence of LVMD in ESRD patients with normal gated stress myocardial perfusion imaging and normal QRS duration (<120 ms) on the surface electrocardiogram. Statistically significant higher values of phase parameters were observed in the studied cohort. Phase analysis using QPS-QGS program revealed, LVMD in a significant number of ESRD patients in the absence of electrical dyssynchrony. There was predisposition of higher incidence of LVMD with

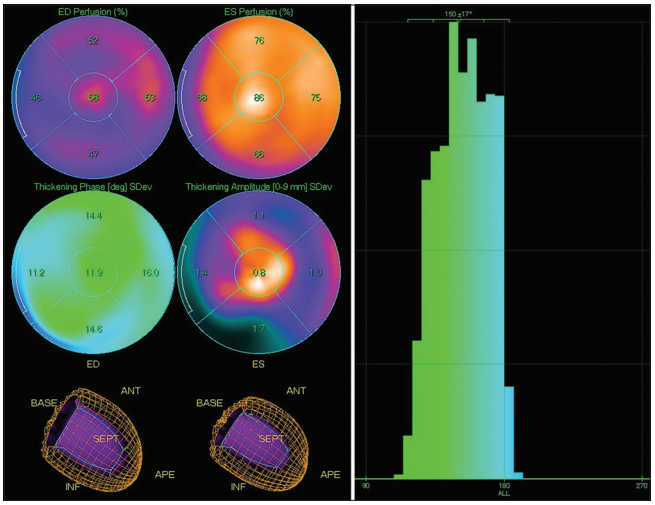

Figure 1: The representative dataset of a patient with ESRD with significant LVMD as suggested by the high PSD and PBW value (17° and 66° respectively) in the absence of any perfusion defect and preserved LV ejection fraction (~54%) and entropy observed was 60%

increase in LV myocardial volume. A statistically signification correlation though of moderate magnitude ($r = 0.31–0.47$) was observed between the LV myocardial volume and different phase parameters [Figure 3].

Several echocardiographic (speckle tracking imaging and real-time three dimensional (3D) echocardiography) and cardiac MRI (myocardial tagging, 3D-tagged cardiac magnetic resonance [CMR], strain-coded CMR, and CMR tissue resynchronization imaging) based methods have been used in the past for assessment of LV dyssynchrony. However, echocardiography-based method has not proved effective in improving prediction of cardiac resynchronization therapy (CRT) response as suggested by recently published echocardiography-guided CRT study.[17] While limitations with MRI-based methods include its inability to image patients with implanted devices, cost, and longer examination time.[18] Phase analysis was first developed in 2005, and subsequent investigators were able to predict the CRT response in the population with ischemic and nonischemic cardiomyopathy using phase analysis of gated SPECT-MPI.[10,19,20]

Aljaroudi *et al*. in their study in ESRD patients had shown the higher values of phase parameters with significant LVMD in ESRD patients compared to the control group, similar to the present study, even in the absence of electrical dyssynchrony and abnormal LV perfusion or function.[21] However, 48% of ESRD patients in their study were suffering from type II diabetes mellitus, that itself was a confounding factor for the presence of LVMD observed in the study from Malik *et.al*.[22] None of the patients in our study had diabetes mellitus thus eliminating its additive influence on phase parameters despite that LVMD was present in a significant number of ESRD patients (28%). Aljaroudi *et al*. did a meticulous study showing the impact of LVMD on cardiovascular outcomes in ESRD patients, where patients with higher PBW values (>62°) had poorer survival. Two-year mortality rate was four to seven times higher in patients with PBW >62° but with no additional high-risk features.[14] Although Hage *et al*. had previously reported that the prolonged QRS (electrical dyssynchrony) was not associated with worse survival in patients with ESRD.[23] These observations showed that LVMD is a better indicator of mortality than QRS duration and may have a role in risk-stratifying the patients.

Furthermore, a study involving the large cohort (more than 800 patients) had shown that LVMD indices (especially PBW) were independently associated with all-cause mortality and provided prognostic information beyond traditional MPI variables.[24] LVMD has marked deleterious effects on

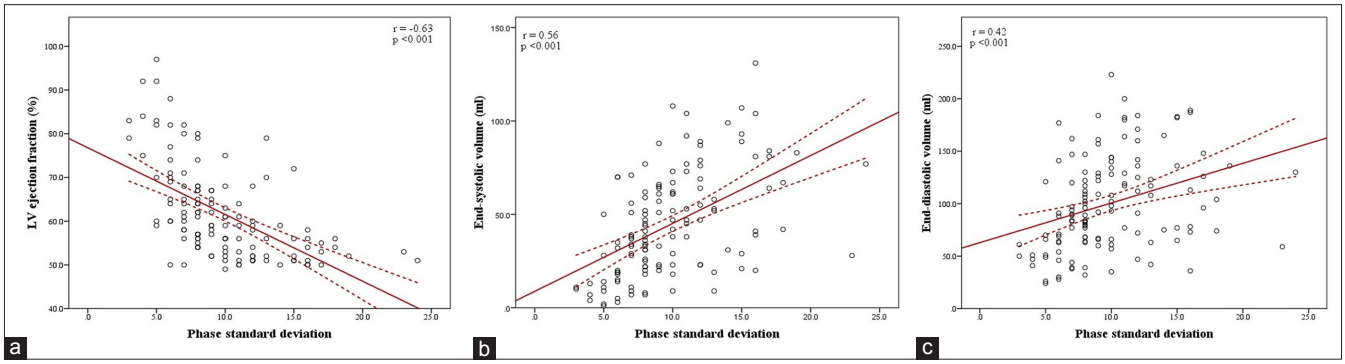

Figure 2: Scatter plot diagrams showing the relationship of phase standard deviation with LV ejection fraction (a), end-systolic volume (b), and end-diastolic volume (c), using QPS-QGS program. The red line represents the regression line, and dotted red lines indicate 95% confidence limits for the regression line

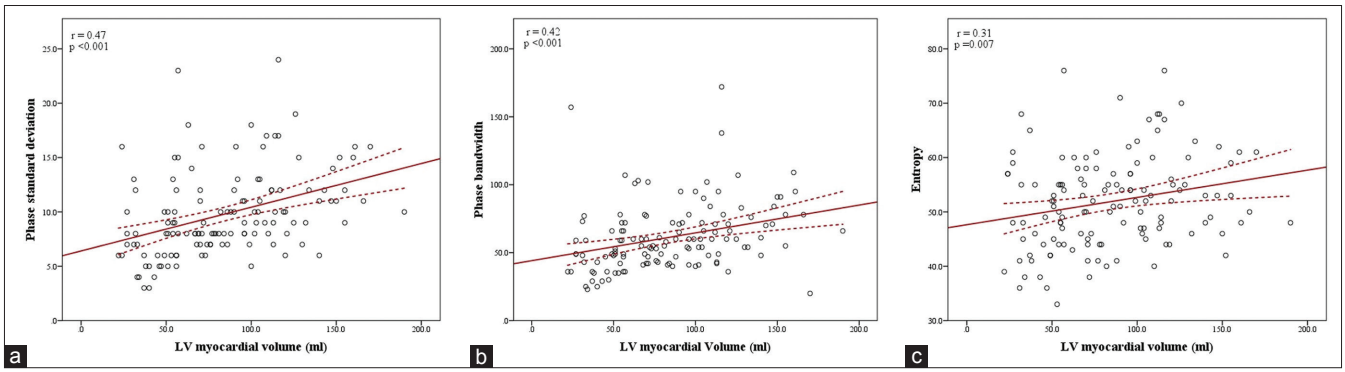

Figure 3: Scatter plot diagrams showing the relationship of attenuated corrected LV myocardial volume with phase standard deviation (a), phase bandwidth (b), and entropy (c) using QPS-QGS program. The red line represents the regression line, and dotted red lines indicate 95% confidence limits for the regression line

ventricular pump function leading to prolonged contraction and reduced ejection time, delayed relaxation with reduced diastolic filling time and arrhythmia susceptibility.[25] The presence of LVMD in ESRD patients may have the potential to contribute to the high incidence of cardiac events or deaths in this group. The main mechanism responsible for LVMD in these patients is not well understood but has been attributed to the presence of chronic volume overload and pulmonary venous hypertension which in turn leads to the right ventricular dilation, septal wall flattening with abnormal contraction and LV hypertrophy.[7] The present study demonstrated the increased incidence of LVMD with increase in LV myocardial volume. A recent study using echocardiography showed that some of the indices of LVMD were preload dependent and could be improved with hemodialysis.[26] However, no such study has been published using phase analysis. Furthermore, Wali *et al*. had shown that renal recipients with pretransplant LVEF <40% and congestive heart failure (CHF) showed significant improvement in LVEF at 12 months of posttransplant period using multigated radionuclide ventriculography. Posttransplant patients showed higher LVEF, better CHF grade, and increased survival with reversal of systolic heart failure.[27] It would be interesting to explore further the effect of renal transplant on the indices of phase analysis in this cohort of patients where around one-third of patients with ESRD had significant LVMD shown by the present study.

CONCLUSION

The present study revealed LVMD in significant number of patients with ESRD in the absence of perfusion defect(s) and normal QRS duration. Attenuated-corrected LV myocardial volume was found to be significantly correlated with phase parameter (PSD, PBW, and entropy) showing that, there was increase in the incidence of LVMD with increase in LV myocardial mass in patients with ESRD. It may be recommended that phase analysis parameters be incorporated in SPECT-MPI reporting as risk stratification in ESRD patients, who undergo gated SPECT-MPI in their pretransplant workup.

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Conflicts of interest
There are no conflicts of interest.

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